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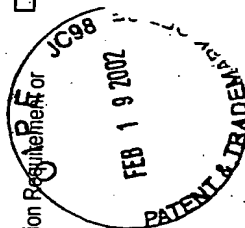
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Inventor: Mizako MIZUNO et al. Appln. No.: 09/577,657 Filing Date: May 25, 2000
Docket No.: 029430-454 Work Atty.: RGM/NEK/jsw Date: February 19, 2002

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2 /31

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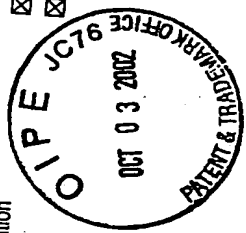
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33

GENES V

Benjamin Lewin

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A special initiator tRNA starts the polypeptide chain

What initiates protein synthesis: how is the first codon of the gene recognized as providing the starting point for translation? The reaction takes place in two stages.

- ◆ The sequence of the ribosome-binding site on a bacterial mRNA is recognized by a 30S subunit carrying IF-3. The part of the site recognized directly by the ribosome is called the **Shine-Dalgarno sequence**; we discuss the interaction between this sequence and the ribosome in Chapter 9.

- ◆ The ribosome-binding site also contains a signal that marks the start of the reading frame, a special **initiation codon**. Usually the initiation codon is the triplet AUG, but in bacteria, GUG or UUG are also used.

The AUG codon represents methionine, and two types of tRNA can carry this amino acid. One is used for initiation, the other for recognizing AUG codons during elongation.

In bacteria and in eukaryotic organelles, the initiator tRNA carries a methionine residue that has been formylated on its amino group, forming a molecule of *N*-formyl-methionyl-tRNA. The tRNA is known as $\text{tRNA}_f^{\text{Met}}$. The name of the aminoacyl-tRNA is usually abbreviated to fMet-tRNA_f.

The initiator tRNA gains its modified amino acid in a two stage reaction. First, it is charged with the amino acid to generate Met-tRNA_f; then the formylation reaction shown in Figure 7.15 blocks the free NH₂ group. Although the blocked amino acid group would prevent the initiator from participating in chain elongation, it does not interfere with the ability to initiate a protein.

This tRNA is used only for initiation. It recognizes the codons AUG or GUG (occasionally UUG). The codons are not recognized equally well: the extent of initiation declines about half when AUG is replaced by GUG, and declines by about half yet again when UUG is employed.

The species responsible for recognizing AUG codons in internal locations is $\text{tRNA}_m^{\text{Met}}$. *This tRNA responds only to internal AUG codons.* Its methionine cannot be formylated.

Thus there are two differences between the initiating and elongating Met-tRNAs: the tRNA moieties themselves are different; and the amino acids differ in the state of the amino group.

The meaning of the AUG and GUG codons depends on their context. When the AUG codon is used for initiation, it is read as formyl-methionine; when used within the coding region, it represents methionine. The meaning of the GUG codon is even more dependent on its location. When present as the *first* codon, it is read via the initiation reaction as formyl-methionine. Yet when present *within* a gene, it is read by Val-tRNA, one of the regular members of the tRNA set, to provide valine as required by the genetic code (see Figure 7.9).

How is the context of AUG and GUG codons interpreted? Figure 7.16 illustrates the decisive role of the ribosome.

Figure 7.15

The initiator *N*-formyl-methionyl-tRNA (fMet-tRNA_f) is generated by formylation of methionyl-tRNA, using formyl-tetrahydrofolate as cofactor.

